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Naïve T Cells in Immunosuppression Diseases: Human Immunodeficiency Virus and Cytomegalovirus

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Dynamic changes of naïve T cells determine mature T cells activity in cell-mediated immune response. It is important to understand the mechanism of homeostasis maintenance affect response to novel antigen toward T cell receptor-major histocompatibility complex interaction. Most of the analysis of naïve T cells relies on flow cytometric immunophenotyping to observe surface antigen alteration within maturation stage. The combination of different surface molecules, such as the cluster of differentiation 62L (CD62L), C-C chemokine receptor type 7 (CCR7), CD27, CD28, and CD45, can give satisfied discrimination between naïve T cells and other subsets. This parameter can be used to monitor the dynamic change of naïve T cells in some chronic diseases, like human immunodeficiency virus (HIV) and cytomegalovirus (CMV). Most of the patient experience loss of naive T cells due to a chronic immune response, which related to apoptotic induction in proliferating cells by viral activity. Some pathogens trigger the migration of naive T cells into lymph nodes to facilitate direct contact with the host cells. The virus infects the cells, use cells proliferation to multiply, and induce apoptosis of host cells after the virions released. Alteration of naive T cells in chronic disease becomes a parameter to oversee the treatment and to determine the future prognosis of the disease. In highly active antiretroviral therapy for HIV infection, observation of naïve T cells and combination of surface molecules, $CD45RO^-$ and $CD27^+$ is used to show the improvement and proliferation rate of total naïve T cells. On the other hand, the transformation of naïve T cells into CMV-specific T cells become really important in CMV prognosis. These conditions suggest that dynamic change of naïve T cells affect to the clinical condition of chronic disease patients.

Keywords: naïve T cells, immunophenotyping, HIV, CMV

Introduction

An adult human is able to produce more than one million blood cells every second on a homeostatic condition in bone marrow. Hematopoietic stem cells (HSCs) develop into erythrocytes, platelets, myeloid cells, mast cells, leukocytes and dendritic cells (DCs).[1,2] The balance of the hematopoietic system is carried out with continuous regeneration by HSCs to meet the body's need to replace short-lived cells.[3]

Leukocytes are the core of the immune system and derived from multipotent HSCs.[4] Leukocytes are classified

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as lymphocytes and myeloid cells.[5] Lymphocytes are divided into T, B and natural killer (NK) cells, which function in cell-mediated immunity. T cells have a big role in adaptive immunity, which directly contacts with foreign particles and eliminates them by cytotoxic activity, or process cytokine to induce activation of particular cells that protect the body.[6] Cytokine is recognized by microparticles as an intracellular communication implication in disease.[7]

HSCs develop into naïve T cells, which are released by thymus in condition with the absence of antigen.[8] Naïve T cells circulate in the bloodstream and move into different lymph nodes to initiate the introduction of antigen. Foreign particles carry unique antigen peptides which can be recognized by T cells receptor (TCR) with the mediation of antigen presenting cells (APCs), such as dendritic cells, macrophage, or B cells. APCs bind the peptides with major histocompatibility complex (MHC), move toward T cells, and create simultaneous signal to trigger the activation of T cells.[9] Activated T cells will differentiate into heterogeneous population depends on the expression of homing molecules.[10]

Maturation of naïve T cells change them into one of the cluster of differentiation 4^+ ($CD4^+$)$CD8^-$ or $CD4^-CD8^+$ cells and finally released from thymus to peripheral tissue.[8] Double positive $CD4^+CD8^+$ cells that interact well with MHC class I will mature into $CD8^+$ cells, whereas the ones interact with MHC class II molecules become $CD4^+$ cells. Cytokines are crucial in the differentiation of T cells lineages by influencing the transcription factors and epigenetic of the cells.[4]

T cells are divided into effector cell (T_{EF}) and memory cell (T_M). T_{EF} is a wide group of active T cells that include helper (T_H), cytotoxic (T_C) and regulatory T (T_{REG}) cells. T_H cells assist other leukocytes in the immunologic process. T_H helps the maturation of B cells and the activation of macrophage and T_C cells. T_H cell expresses CD4 which directly contact with MHC class II on the surface of APC and release cytokines.[4,8] Furthermore, T_C cell will recognize the target cell through the interaction of CD8 receptor and MHC class I molecule. T_C cell releases perforin and interferon (IFN)-γ to induce apoptosis of the target cell.[11] At the end of immune response, T_{REG} cell will produce interleukin (IL)-10, adenosine and other signaling molecules to inactivate T_C cell in preventing autoimmune diseases. Survived T cell serves as T_M cell to response the same antigen for the second infection. They rapidly expand to T^{EF} cell upon re-exposure to cognate antigen.[8]

T Cells Homeostasis: Mechanism of T Cells Maturation

A Most mature naïve T cells are maintained without proliferating and remain fairly constant in the periphery. These mature T cells pool is regulated by complex homeostasis mechanism. Homeostasis needs to preserve as a way to ensuring balanced loss and replacement of peripheral naïve T cells. Naïve T cells pool maintain the diversity of unique antigen receptors in limited space by extrinsic survival cues. MHC complex is crucial to maintaining the homeostasis of naïve T cells pool, which the expression of MHC molecule is necessary for the preservation of double phenotype naïve T cell into mature $CD8^+$ or $CD4^+$ T cell.[6,8] These stimuli give potential changes in characteristics which vary depending on TCR intensity and competition between naïve T cells in the thymus. However, the competition in naïve T cells pool is still unclear since specificity of each cell is affected by various factors.

A distinct pattern of T cells competition has been reported as potential mechanism to sustain T cells diversity. Some studies suggest that T cells with the same specificity compete for each other towards same self-peptide-MHC complexes, when other T cells are unaffected (Figure 1a).[12] This model has limited access to self-peptide-MHC complexes in order to control the size of the T cells pool and restrict the effect of intraclonal competition. It is proven by the transfer of low frequency of monoclonal, TCR-transgenic $CD4^+$ resulted in longer survival for the T cell than seeded in higher frequency in a normal environment.[13] This led to an improvement in $CD4^+$ T cells pool donor which suggest that homeostasis of the naïve T cell pool produces an optimal number of T cells with the same specificity.[14]

In contrast, other studies suggest the competition within different specificities. TCR diversity allowed each of T cell to compete for various non-specific self-peptide-MHC ligands. TCR of one population could interact with self-peptide-MHC complexes that support the different T cells specificity (Figure 1b).[15,16] Competition between different specificity of T cells allows a domination of one clone over another to react with self-peptide-MHC in the present of external supports, such as survival factors (Figure 1c).[16] In this case, TCR engagements within the cells are not equivalent. Stronger naïve T cells are more effectively to compete and leave weak cells to die by apoptosis.

Some previous studies found an interesting fact that CD5 correlate with the regulation of competition hierarchy

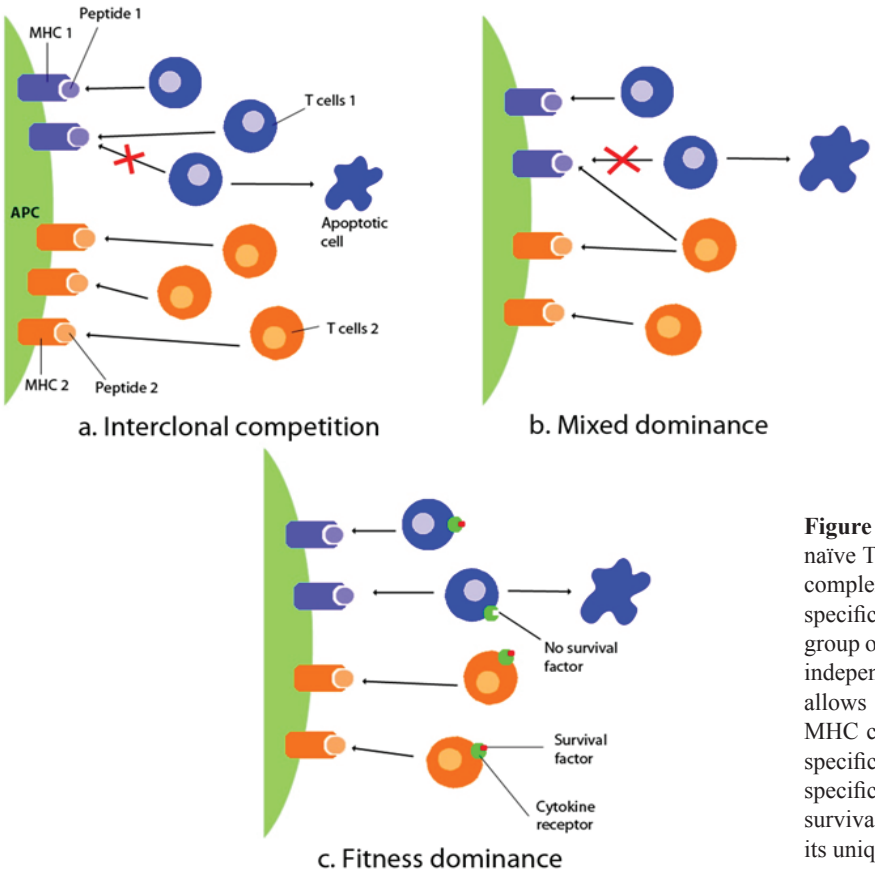

Figure 1. Naïve T cells competition. Model of naïve T cells competition towards self-peptide-MHC complexes. a) Interclonal competition of the same specificity in the same pool. In this model, each group of naïve T cells maintenance of these two pools independently. b) Mixed TCR of one population allows them to compete in different self-peptide-MHC complexes, limiting the T cell space for other specificities. c) This model is allowing T cells of one specificity to more effectively compete for a limited survival factor (such as cytokine) when interacting to its unique self-peptide-MHC complexes.

of TCR. CD5 is a negative regulator of lymphocyte receptor signaling. CD5 expression was found higher in stronger TCR signaling intensity and showed superior homeostatic properties than any other cells. $CD5^{hi}$ naïve T cells proved that stronger sensitivity of TCR gives the best survive chance in selection mechanism by self-peptide-MHC complexes.[17] The dominance of superior naïve T cell is affected by limiting factors (*e.g.,* intraclonal competition) to prevent complete domination even the cells have competitive advantage. These models may lack in some interpretations since most of the studies occur in lymphopenic condition that radically altered T cells homeostasis. However, they provide a fascinating explanation of how MHC specificity may affect competitive survival of naïve T cells in polyclonal pool.

Based on several previous studies, the effect of self-peptide-MHC complexes on sensitivity to foreign antigen is still arguable. One study showed positive correlation between naïve $CD4^+$ T cells with self-peptide-MHC complexes. In this study, *in vivo* naïve $CD4^+$ T cells which lack MHC class II molecules showed low proliferation rate and IL-2 production in *in vitro* simulation of antigen-MHC class II.[18] This emphasizes how self-peptide-MHC complexes capable of supporting naïve T cells sensitivity towards antigenic stimulation. In another hand, other studies have reported that loss of self-peptide-MHC class II complexes enhanced early activation of $CD4^+$ T cells. MHC-TCR binding elevates CD5 expression in CD4 naïve T cell and increases the strength of MHC interaction. However, this interaction triggers a reduction in response to TCR signaling.[19] This shows the correlation between the regulation of CD5 expression and TCR response in order to induce the activation of naïve T cell activation.

In CD8 T cells, activation and expression of the cells are controlled by self-peptide-MHC class I complexes in order to discriminate antigen specificity. In MHC class I deficient mice, transferred $CD8^+$ T cells just showed responsiveness to weak foreign peptide due to *in vivo* response to DCs even in lack of MHC class I molecule.[20] Following this condition, $CD8^+$ cells showed normal proliferation rate and an improvement in IFN-γ production to secondary stimulation, while continuous contact with self-peptide-MHC complexes triggers activation threshold.[21] This concept might serve as prevention to auto-reactive T cells.

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Naïve CD4 T cell response is also related to T cell's motility. $CD4^+$ T cells have to move properly in lymph nodes to detect the existence of DCs. Declining of Ras-proximate-1 (RAP1) and Ras-related C3 botulinum toxin substrate 1 (RAC1), which act as guanosine triphosphatase to regulate actin cytoskeleton and adhesion molecules in lymphocyte movement, give great impact to cells motility.[22] These models show a promising mechanism to understand how TCR sensitivity affect naïve T cells to react to the presence of foreign antigen in lymph nodes. It raises an issue to determine the effect of self-peptide-MHC complexes with various physiological in vivo properties for clear interpretation.

Naïve T cells Immunophenotyping

Activated naïve T cells differentiate into T_{EF} subsets and T_M subsets. Unfortunately, the alteration of T cells within the immune response doesn't indicate any mutation in the receptor genes and cell structure; however, the changes only occur in cells phenotype. It's hard to differentiate those cells in gene-based analysis and morphologically, but not in cytometry analysis. Flow cytometry is an accurate instrument to distinguish specific cell within a population based on surface antigen expression, including T lymphocytes subsets.

Naïve T cells express CD62L and C-C chemokine receptor type 7 (CCR7)/CD197, which are useful parameters to discriminate naive T cell with T_M cell. CD62L and CCR7 are adhesion molecules that involved in naïve T cells migration through the lymph nodes via high endothelial venules (HEV). CD62L and CCR7 respectively bind to surface vascular addressin and chemokines on the surface of HEV in peripheral blood.[23] In contrast to the naïve T cells, these molecules are expressed differently in T_M subsets, $CD62L^+CCR7^+$ express on central memory (T_{CM}) cell and $CD62L^-CCR7^-$ on effector memory (TEM) cell.[24] TEM cell lacks CD62L and CCR7 because the cell's migration doesn't pass the HEV, but circulate through the network of extra-lymphoid tissue. In the expansion of T cells, these memory cells will express perforin and IFN-γ in high concentration in the second response, indicates the cells already differentiated into activated T_{EF}.[11]

Other surface molecules that used to distinguish naïve T cells and T_M are CD44, Ly6C, CD122 (IL-2 β-chain) and CD45 (common leukocyte antigen).9,25 Naïve T cells do not express CD44, Ly6C and CD122, but they slowly expressed later in the initiate phase of T_M cells formation. T_M strongly expresses these three molecules, both on T_{CM} and T_{EM} subsets. Ly6C weakly expressed on T_{EF}, so that these parameters can be used to distinguish TM $CD8^+$ with T_{EF}.[25] CD45 is a tyrosine phosphatase which has role in regulating signaling molecules through antigen and chemokine receptors.[9] CD45 used to discriminate naïve T cells to T_M based on the existence of splicing regions of each isoform. High molecular weight CD45 isoform or CD45RA is expressed on the cell with low division rate and low response to the antigen. At the activated state, these cells lost CD45RA molecules and replaced with low molecular weight isoform, CD45RO, which has no exons (A, B, C exon). The population of CD45RO tends to divide rapidly and more responsive to the antigen.[11]

CD27 and CD28 are effectively discriminate between naïve and TEF $CD8^+$. CD28 and CD27 serve as co-stimulator in the cell adhesion and signaling molecules between APC and TCR.[25] These molecules expression will slowly down-regulated after TCR stimulation or on late differentiated cells.[26,27] Studies in mice showed that cell which lack of CD27 and CD28 has great potential to produce perforin and granzyme to induce apoptosis in infected cells.[28] In the human cytomegalovirus (HCMV) carrier, clone of T cells which distributed into two subpopulations, $CD27^+$ $CD28^-$ $CD11a^{hi}$ and $CD27^-$ $CD28^-$ $CD11a^{hi}$, showed high cytotoxic activity that indicates the potential of T_{EF}. Upregulation of CD11a also occurs on T_{CM}, but not in naïve T cells, which have $CD11a^{lo}$.[29]

Alteration of Naïve T Cells in HIV & CMV

The body will expose to a lot of antigens that decrease the quantity and quality of immune cells as a result of the increasing proportion of antigen-experienced cells.[30] The morbidity and mortality of the disease will increase in the elders coincide with involution of immune organs or immunosuppression agents. Immunosuppression is a state when the immune system is reduced in certain conditions by external factors, *e.g.,* rejection after donor transplant, chemical therapy or mostly due to bacterial/viral infection. Immunosuppression is a serious condition which makes the immune system can't act as normal host defense system, which called immunologic deficiency. There are two common categorize of immune deficiency: primary immunodeficiencies (PI) and secondary immunodeficiencies (SI).[31] PI are manifest early in life as repeated infections in

normal children. In the chronic state, PI can be a serious disease which affects a single or multiple parts of the immune system. These diseases are caused by hereditary or genetic defect which results in immune abnormalities and infection susceptibility.[32] In the other hand, SI arises outside of the immune system and not restricted only to immune elements (multisystem biochemical defect and nutritional deficiency that have possibility to depress immune system are included). SI commonly occurs in older age group, characterized by excessive loss of lymphocytes.[31]

Dysregulation of various lymphocyte precursor cells causes disruption of population, function and homeostasis condition of the immune system, especially on T cells and B cells.[33] Viral and bacterial exotoxins can induce over-exploitation of lymphocytes. Approximately 20% of lymphocytes are stimulated by exotoxins which lead to chronic inflammation and fatal condition, like sepsis.[34] Damage of T cells is also correlated to age-related effects in immune system. Transfer of young T cells in old mice showed improvement in antibody production, compared with non-treatment old mice. In contrast, young mice which had received old T cells exhibited a reduction in B cells response and antibody production. This is presumably due to the decreased expression of CD40 ligand associated with APC that affect in mediated immune system.[35]

As explained previously, exposure to foreign antigens continuously can reduce the number of naïve T cells among total T cells. The rate of naïve T cells alteration is different in each individual, connected to several factors, such as genetics, nutrition or environmental conditions which support the spread of infectious diseases. Individuals in certain population will show lymphocyte phenotype differently from other populations. The comparative study on non-human immunodeficiency virus (HIV) Dutch and Ethiopia population found significant differences in lymphocyte number. Ethiopian population tends to have fewer in the total of naïve T cell, but higher in memory and effector cells.[36] In another study, comparative of naïve T cells number between Malawi and UK population showed distinction pattern, both in respondents with CMV seropositive & seronegative. CMV seropositive in UK population showed a higher number of naïve T cells even compared with healthy Malawian.[37] This phenomenon occurs due to the high risk of infectious diseases, such as malaria, CMV and HIV, faced by the African. The decline in naïve T cells associated with the accumulation of memory and effector T cells that don't have a co-stimulatory molecule of CD28. CD28 plays an important role in the ligation between T cells to target tissue in the immune response.[38]

Naïve T cells alteration in HIV patients

Wild-type HIV is a subgroup of retrovirus that causes acquired immunodeficiency syndrome (AIDS). People with AIDS are threatened by opportunistic infections and cancers due to progressive failure of the immune system. According to The Joint United Nations Programme on HIV/AIDS (UNAIDS), there are more than 45 million people have been infected, and over 90% live in developing countries. HIV can be transmitted via blood, genital fluid and breast milk in free virus particles and infected cells form. HIV can infect T lymphocytes (mostly T_H cells), dendritic and macrophage cells. The viral infection mechanism occurs through apoptosis of infected cell, pyroptosis, direct killing or using T_C cell to kill T_H cell. Infected patients able to life longer as normal human with intensive treatment, but the survival rate drops to 9-11 years on the untreated patient.[39]

Monitoring the level of T cells in HIV patients can be used to study the mechanisms of infection and T cell depletion in a comprehensive manner. Alteration in T cells during the infection phase can be measured using the T cell receptor excision circles (TRECs) which represent the function of the thymus organ.[40,41] Reduction the number of naïve T cell on HIV patients due to hyperactivation of the immune system, lead to increasing the number of memory cells that lack to response with new antigens.[42] HIV type-1 enhances the priming of naïve T cell by inducing chronic immune activation and boost up the proliferation rate. At the same time, the decline in naïve T cells by HIV type-1 will be applicable as a homeostatic mechanism that aims to keep the number of naïve T cells remains constant at the current rate when proliferation phase continue revolving.[43]

The death rate of T cells also detected during HIV type-1 infection.[44] On steady-state conditions, virus in the lymphoid tissues might provide signals resembling lymphocyte homing and circulation mechanism. This signal is up-regulating the homing receptor of CD62L that triggers naïve and central memory T cells to migrate toward the lymphoid tissue. Regulation of CD62L was also supported by signal molecules from the abortive cell, an unstable cell that carries certain virus which unable to enter the host cell nucleus. Through CD62L, virions or virus-producing cells may provide signals to target cells that trigger apoptosis.[45,47] Infected cells can last for two days before death to produce more viral progeny.[46] Meanwhile, proviral can last several months or years and usually found in latent infection.[47]

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Latent infection is suspected to be correlated with the presence of naïve T cells because the longevity of naïve T cells and the ability of naïve T cells to proliferate & differentiate to another cell to help viral multiplying. Naïve T cell differentiation makes biased detection of latent infection source that was allegedly formed from central memory T cells or effector memory transition T cells.[48]

Naïve T cells alteration in CMV infection

CMV is a herpes virus with a world seroprevalence ranging from 45-100%. In immunocompromised patient, viral acquisition occurs via reactivation of latent infection or primary infection. Congenital CMV affects 0.6-0.7% of live births in industrialized countries with 10% of the population show symptomatic disease, such as microcephaly or deafness, and 4% die during the newborn period. Hereafter, primary CMV is the most common infection after organ transplantation. Patient with CMV shows several clinical syndromes, *e.g.,* encephalitis, pneumonitis, hepatitis, uveitis, retinitis and colitis. In healthy adults, the viral particles become latent, self-limiting into lifelong bloodborne virus.[49]

CMV infection is known to cause end-stage differentiation and replicative senescence of T lymphocytes and lead to increasing risk of infectious diseases, degenerative conditions and neoplasm abnormality.[50] Patients with CMV seropositive have lower percentage of naïve T cells, but showed an escalation in the proportion of $CD28^-$ $CD45RO^+$ memory cells.[37] CMV seropositivity was associated with oligoclonal expansion in differentiated $CD28^-$ $CD57^+$ T cells. The appearance of these cells indicates the reduction of naïve and memory T cell response against other antigens.[51] Some cases in adults (aged 19-55 years), patient with CMV seropositive showed 10% of T cells with CMV-specific phenotype within overall number of CD4 and CD8 T cells[52] as the mechanisms from the virus to suppress the diversity and function of T cells. Latent infection can show no symptoms in immunocompetent person, but with substantial change, it can be dangerous for patients with immunocompromised conditions. This is associated with "immune risk people" (IRP) which inducing high risk of mortality due to fragile immune response.

IRP does not always portend to poor prognosis, but with aging, CMV progressively creates higher viral replication. Antigen stimulation will gradually improve the number of CMV specifics T cell, trigger cell dysfunction due to excessive activity of non-senescence T cells, and then replace the functional T cells with new poor generation. Viral replication will suppress the population of naïve and memory T cells by creating a chronic inflammatory condition, lead to disrupting T cells homeostasis.[53] This condition in will be maintained by the virus at the same level as chronic immune suppression of viral infection, such as HIV.[52] On immunocompetent patient, relapse of CMV infection is suggested by the existence of CMV-specific memory T cells. Basically, CMV-specific T cells functionally working to response CMV activity and keep them in resting state. In many cases of CMV, there was no obvious symptom to specific disease, although CMV has a high reactivity after immunosuppressive therapy.[54]

CMV pathogenicity may be affected by intrinsic senescence mechanisms of CMV-specific T cells. CMV-specific T cells have shorter telomeres character and high mutation rate to make these cells life is very short. One of the possibilities why the frequency of CMV relapse is increasing. CMV-specific T cell populations replace the naïve cell and memory cell pools that interfere T cells homeostasis. At some points, when body reach a lower condition of immune system, it will be an opportunity for CMV to out from resting state and boost their replication. CMV replication followed by other infectious complications may increase mortality of patients.[54] On the other hand, there is a counter-argument of the role of CMV-specific T cells in immune suppression. CMV-specific T cells are just a few of the total T cells found in lymph nodes that are not capable of replacing the naïve and memory T cell pools. Replicative senescence and some 'abnormal' conditions can also be found in the pattern of differentiation of effector memory cells in all ages, younger or older.[55] For the alternative scenario, replication of CMV and CMV-specific response in each individual are initiated by age-related diseases.[54]

Determining Prognosis of Highly Active Antiretroviral Therapy (HAART)

HAART is a new breakthrough in the restoration of CD4 T cells in HIV infection. Immunophenotyping of naïve T cells is useful in the post-therapy monitoring while learning about HIV pathogenicity. This treatment proved capable of reducing viral load, expand the survival rate, and less painful than any other treatment. Unfortunately, the limit of availability and the high cost of the medicine are the main consideration to the implementation of HAART in some countries. In addition, resistance to viral drug and

ineffective outcome of HAART had been found in certain patients.[56,57]

In the first study, patients will receive a combination of drugs at the initiation of therapy, such as indinavir, nevirapine, lamivudine, zidovudine, and/or stavudine. Within a certain time during the duration of therapy, respondent will go through a series of test to observe naïve T cells ($CD45RO^-$ and $CD27^+$), memory T cells ($CD45RO^+$ and $CD27^-$), effector T cells CD4 ($CD45RO^+$ and $CD27^-$), and effector T cells CD8 ($CD45RO^{+/-}$ and $CD27^-$). Proliferation level of CD4 and CD8 was analyzed by Ki67 staining and dynamic change on T cells with $CD4^+$ $CD45RO^-$ dan $CD8^+$ $CD45RO^-$ was measured with 5-bromo-2'-deoxyuridine (BrdU). The results showed significant increase in the number of naïve T cells CD4 and CD8 with a reduction of cell proliferation level by Ki67 staining. Kinetic change on naïve T cells with BrdU showed lower level of cell proliferation and apoptosis rate after six months treatment with HAART.[41]

A decrease in the proliferation level which proportional with cell death rate explained that priming T cells into memory T cells are related with reduction of naïve T cells in HIV infection. Normalization of T cells also associated with the increase in the population of naïve CD4 and CD8 T cells, although the CD4 T cells showed better outcome than CD8 T cells. This is indicating the independent mechanism between CD4 and CD8 T cells. With this model study, TRECs outcome showed similar mechanism in the priming stage of naïve T cells into memory cells in both populations, but the naïve CD4 T cells exhibited higher cell death rates than CD8 T cells. This discovery supports earlier theory about the preference of HIV type-1 infection to interfere naïve CD4 T cells.[58] Observations on ligand-mediated apoptosis in the acute immunodeficiency simian virus (SIV) indicate large amounts of virions exposure in the $CD4^+$ T lymphocytes, but not in $CD8^+$.[59] A theory that maybe supports this outcome is the nature of the CD4 T cells which has higher levels of proliferation rate than CD8 T cells.[41]

As mentioned earlier, in some cases, HAART treatment did not show significant progress towards CD4 population, although the treatment showed a promising result to suppress the viral replication.[57] Damage to the reticular fibroblastic cell (FRC) is one of the possible reasons to reduce T cells restoration during the treatment with HAART. FRC serves as migration pathway for naïve T cells to access various survival factors, such as Interleukin-7 (IL-7). Damaged FRC increase cell apoptosis rate and decrease the recovery of T cells after treatment with HAART.[60] Animal models with SIV with suffered lymphoid tissue as a result of collagen disposition showed increased in cell apoptosis of naïve CD4 and CD8 T cells. This is associated with an incapability naïve T cells to access IL-7.[61] Lymphoid tissue fibrosis is progressive and accumulative. Treatment of HAART should be applied early as possible when collagen disposition and FRC damage still on low level.[62] It will increase the probability of successful treatment.

At more advanced stage, accumulation of damage in lymphoid tissue with increased collagen deposition and disruption of FRC in chronic infection. Reconstruction of naïve T cell will be worse in older patients. Involution of thymus and degeneration of thymic function limit the pace and the restoration rate of naïve T cells.[63] Therapeutic approach to restoring the lymphoid tissues and FRC is important to improve effectiveness of HAART. Therapeutic use of IL-7 in conjunction with HAART in HIV and SIV infection can significantly increase the number of naïve CD4 T cells. However, a decrease in CD4 and CD8 naïve T cells number occurs after terminate the IL-7 therapy. This indicating that the therapeutic effect of IL-7 is just temporary.[63,64] For further development, the application of anti-fibrotic therapy in FRC and lymphoid tissues, like pirfenidone and losartan, may be used as lymphoid tissue reconstruction.[62,63]

Maintain CMV Infection

CMV infection is benign in immunocompetent patient and has to maintain with specific T cell response control in order to keep the virus in the latent phase. With aging, immune senescence occurs correlated with persistent of CMV infection. CMV infection will induce the production of CMV-specific T cells as a response of immune system to maintain viral infection. CMV-specific T cells characterize by effector memory phenotype ($CD28^-$, $CD27^-$, $CCR7^-$), reduce CD4/CD8 ratio and loss in naive T cell number.[54] In immunocompromised people, this condition causes a higher chance of opportunistic infection, such as enteritis and pneumonia. Accordance with those conditions, obviously, CMV-specific T cell is culpable in the development of immune senescence.[65]

CMV-specific T cell may change the immune system composition, but its response still needed to maintain viral replication. Unfortunately, CMV-specific T cell response deteriorates in IRP, allowing more frequent of

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viral replication. In some previous studies, there are some explanations how CMV-specific T cell has roles in maintain CMV infection. CMV-specific T cells are widely used to prevent of viral infection after hematopoietic stem cell transplantation.[65,66] CMV-specific cells can be developed from naïve T cells from umbilical cord blood (UCB) or donors with CMV seronegative. Based on the principle of multi virus-specific T cells, naïve donor T cells will create the CMV-specific T cell lines from UCB. Isolation of naïve T cells is performed by eliminating the memory cells and the presence of other viral antigens to increase the specificity of the CMVpp65. CMVpp65 a typical epitope commonly detected in human leukocyte antigen (HLA)-A2 positive donor.[67] Naïve T cells from the donor can also recognize atypical (less common) CMVpp65 epitope for improving the availability of CMV-specific T cells in patients with high risk of CMV. The ability of T cells to recognize atypical CMV epitope is suspected as an *in vivo* defense mechanism against CMV.[66]

Naïve T cells have the ability to recognize the epitope more than the memory cell. The specific cell will recognize the particular peptide which the expression will vary depend on certain stage. The population will be different at each stage, from initiation to chronic phase.[66,68] T cells response is difficult to detect because of the mixed response against CMV. This change was also influenced by the dynamic change of T cells which be replaced by other T cells over time. Identification of the optimal population of T cells to the donor becomes important in adoptive immunotherapy.[69] Although this therapy is considerably safe and showed low level of viral reactivity after therapy, it's hard to implement this therapy due to complicated mechanism and take more times to perform cell culture.[66]

Conclusion

Naïve T cell is an essential component in the formation of T cell subsets that support the body's immune system. Immunophenotyping naïve T cells can be used to help identify naïve T cells among T cells subsets, such as memory and effector T cells. In the HIV and CMV infection, measurement of naïve T cells may help in understanding the mechanism of infection more comprehensive. The lower level of naïve T cell within the infection period is caused by an increasing of cells apoptosis. Either because of their excessive proliferation or activation of the cell death signal by HIV and CMV viral components. Monitoring naïve T cells population during HAART HIV patients showed the effectiveness of therapies based on the alteration of naïve CD4 and CD8 T cells number. In CMV infection, differentiate naïve T cells into CMV-specific T cells triggers an imbalance of T cell population which lead to increase the vulnerability of other diseases at the same time with the decline of immunity. On the other hand, the CMV-specific T cells serve to maintain the resting state of CMV in better immunocompetent person. With all these explanations, the dynamic change of naïve T cells is an important parameter in multiple infections associated with immunosuppression.

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